

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study



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Summary

Background Oncogenic alterations in *RET* have been identified in multiple tumour types, including 1–2% of non-small-cell lung cancers (NSCLCs). We aimed to assess the safety, tolerability, and antitumour activity of pralsetinib, a highly potent, oral, selective *RET* inhibitor, in patients with *RET* fusion-positive NSCLC.

Methods ARROW is a multi-cohort, open-label, phase 1/2 study done at 71 sites (community and academic cancer centres) in 13 countries (Belgium, China, France, Germany, Hong Kong, Italy, Netherlands, Singapore, South Korea, Spain, Taiwan, the UK, and the USA). Patients aged 18 years or older with locally advanced or metastatic solid tumours, including *RET* fusion-positive NSCLC, and an Eastern Cooperative Oncology Group performance status of 0–2 (later limited to 0–1 in a protocol amendment) were enrolled. In phase 2, patients received 400 mg once-daily oral pralsetinib, and could continue treatment until disease progression, intolerance, withdrawal of consent, or investigator decision. Phase 2 primary endpoints were overall response rate (according to Response Evaluation Criteria in Solid Tumours version 1.1 and assessed by blinded independent central review) and safety. Tumour response was assessed in patients with *RET* fusion-positive NSCLC and centrally adjudicated baseline measurable disease who had received platinum-based chemotherapy or were treatment-naïve because they were ineligible for standard therapy. This ongoing study is registered with ClinicalTrials.gov, NCT03037385, and enrolment of patients with treatment-naïve *RET* fusion-positive NSCLC was ongoing at the time of this interim analysis.

Findings Of 233 patients with *RET* fusion-positive NSCLC enrolled between March 17, 2017, and May 22, 2020 (data cutoff), 92 with previous platinum-based chemotherapy and 29 who were treatment-naïve received pralsetinib before July 11, 2019 (efficacy enrolment cutoff); 87 previously treated patients and 27 treatment-naïve patients had centrally adjudicated baseline measurable disease. Overall responses were recorded in 53 (61%; 95% CI 50–71) of 87 patients with previous platinum-based chemotherapy, including five (6%) patients with a complete response; and 19 (70%; 50–86) of 27 treatment-naïve patients, including three (11%) with a complete response. In 233 patients with *RET* fusion-positive NSCLC, common grade 3 or worse treatment-related adverse events were neutropenia (43 patients [18%]), hypertension (26 [11%]), and anaemia (24 [10%]); there were no treatment-related deaths in this population.

Interpretation Pralsetinib is a new, well-tolerated, promising, once-daily oral treatment option for patients with *RET* fusion-positive NSCLC.

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Introduction

The *RET* proto-oncogene encodes a transmembrane receptor tyrosine kinase (proto-oncogene tyrosine-protein kinase receptor *RET*) that has a physiological role in the embryonic development of the nervous system and the kidneys.¹ Activating alterations in *RET* have been implicated in the molecular pathogenesis of many solid tumours, including thyroid cancer and non-small-cell lung cancer (NSCLC).¹ Chromosomal rearrangements of the *RET* gene occur when the sequence encoding the *RET* intracellular kinase domain becomes linked to the N-terminal, protein dimerisation domain sequence of another protein. These rearrangements permit aberrant expression in cell types in

which *RET* is ordinarily transcriptionally silent, and lead to the generation of oncogenic intracellular *RET* fusion proteins capable of ligand-independent activation.¹

RET fusions are present in 1–2% of NSCLCs¹ and represent an important new therapeutic target. Early clinical trials in *RET* fusion-positive NSCLC evaluated multikinase inhibitors with anti-*RET* activity, including cabozantinib, vandetanib, and lenvatinib, but these agents showed modest clinical activity with high rates of treatment-related toxicity.^{2–5} Nonetheless, clinical data from these studies provided early proof-of-concept that *RET* fusions are targetable drivers in NSCLC, and underscored the need for selective *RET* inhibitors.

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Research in context

Evidence before this study

We searched PubMed for studies published in English between Jan 1, 2015, and July 31, 2020, investigating targeted treatment of *RET* fusion-positive non-small-cell lung cancer (NSCLC). Search terms included “*RET*” plus “NSCLC” and were filtered for clinical trials. Of the nine entries returned, we identified four phase 2 studies reporting treatment outcomes specifically in patients with *RET* fusion-positive NSCLC; two phase 1 trials, a retrospective analysis, a molecular testing study, and a trial protocol article were not considered relevant. All four studies reported on outcomes of multikinase inhibitor treatment in *RET* fusion-positive NSCLC: two studies of vandetanib, one of cabozantinib, and one of lenvatinib. Although these agents showed modest efficacy, with response rates that ranged from 16% to 47% and median progression-free survival ranging from 4.5 to 7.3 months, high levels of toxicity were observed, with 53–73% of patients having dose reductions owing to adverse events. After the data cutoff for the present study but before publication, outcomes from a phase 1/2 study of the *RET* inhibitor selpercatinib in patients with *RET*-altered cancers were reported. Among patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy who received selpercatinib, the response rate was 64% and median progression-free survival was 16.5 months; of all patients who received selpercatinib, including those with tumours other than NSCLC, 30% had dose reductions owing to treatment-related adverse events.

Added value of this study

ARROW is the first prospective study to investigate pralsetinib for the treatment of *RET*-altered solid tumours, including *RET* fusion-positive NSCLC, and the second study to report on outcomes with a selective *RET* inhibitor, following the study of selpercatinib. Our data show that pralsetinib has clinical activity in patients with *RET* fusion-positive NSCLC, with response rates of 61% in patients with previous platinum-based chemotherapy and 70% in treatment-naïve patients who were not candidates for available standard of care. Adverse events were predominantly of grade 1–2 severity, and rates of dose reductions and treatment discontinuations owing to treatment-related adverse events were low. Overall, pralsetinib had a manageable safety profile and showed clinical activity in patients with *RET* fusion-positive NSCLC, irrespective of previous treatment history or fusion partner.

Implications of all the available evidence

Historically, patients with *RET* fusion-positive NSCLC have had very few safe and effective treatment options outside of standard of care available for tumours without targetable oncogenic drivers. The findings from our study show that *RET*-targeted treatment with pralsetinib has antitumour activity in *RET* fusion-positive NSCLC, and has a predictable and manageable safety profile. The utility of *RET*-targeted therapies is also validated by outcomes with selpercatinib, and approval of both agents in the USA provides new treatment options in this patient population.

Pralsetinib (formerly known as BLU-667) is an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic *RET* fusions and mutations, including V804 gatekeeper mutations associated with resistance to multikinase inhibitors, and has shown high selectivity for *RET* over other tyrosine kinases.⁶ Pralsetinib has shown antitumour activity in various preclinical *RET*-altered tumour models, including intracranially implanted tumours.^{6,7} Here, we report on the safety and activity of pralsetinib in patients with *RET* fusion-positive NSCLC from the registrational phase 1/2 study (ARROW), which formed the basis of its US Food and Drug Administration approval for the treatment of metastatic *RET* fusion-positive NSCLC.

Methods

Study design and participants

ARROW is a multi-cohort, open-label, phase 1/2, study of pralsetinib in patients with advanced *RET*-positive solid tumours done at 71 sites (community and academic cancer centres) in 13 countries (Belgium, China, France, Germany, Hong Kong, Italy, the Netherlands, Singapore, South Korea, Spain, Taiwan, the UK, and the USA; appendix pp 3–6). The phase 1 dose escalation part of the trial determined the maximum tolerated dose and

recommended phase 2 dose.⁸ The phase 2 dose expansion part evaluated the safety and activity of pralsetinib in multiple expansion groups (appendix p 19).

Eligible patients were aged 18 years or older with unresectable, locally advanced or metastatic solid tumours, and a pathologically or genetically documented *RET* fusion or mutation. Eligibility for each phase 2 expansion group was primarily defined by disease type and previous therapy status. For inclusion in the *RET* fusion-positive NSCLC groups, patients were required to have locally advanced or metastatic NSCLC, and a documented *RET* fusion per local testing of tumour or circulating tumour nucleic acid (ctDNA) in blood (patients with NSCLC and point mutations in *RET* were eligible for enrolment in a separate group [group 7] and are not included in the currently presented analyses). Before July 11, 2019 (the enrolment cutoff date for efficacy analyses), eligibility was limited to patients who had previously received standard of care treatments or who were treatment-naïve and not candidates for available standard therapies. Subsequently, the protocol was amended to allow enrolment of treatment-naïve patients regardless of eligibility for standard therapies (implemented July 11, 2019). Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0–2 (limited to

0–1 in a protocol amendment after July 25, 2018) and baseline measurable disease by investigator assessment per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1). Patients with untreated CNS metastases were permitted if not associated with progressive neurological symptoms. Patients requiring corticosteroids for management of CNS disease must have been on a stable dose for 2 weeks or more before initiating pralsetinib. Patients with low platelet counts, low neutrophil counts, elevated liver transaminases, elevated bilirubin, reduced creatinine clearance, or elevated serum phosphorus (all within 14 days before first dose of pralsetinib) were excluded. Full eligibility criteria are provided in the protocol (appendix).

This study was done in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki and based on the International Council for Harmonisation E6 requirements. The protocol was approved by the institutional review boards at all sites and all patients provided written, signed, informed consent. Safety was initially monitored by a safety review committee consisting of investigators and sponsor representatives.

Procedures

In the dose-escalation part of the study, patients received pralsetinib orally at doses of 30–600 mg once daily. In the phase 2 dose-expansion part, patients initiated pralsetinib at the recommended phase 2 dose of 400 mg once daily. All patients received pralsetinib until disease progression, intolerance, withdrawal of consent, or investigator decision. Treatment after disease progression was allowed if in the best medical interest of the patient as determined by the investigator. Dose reductions (in 100 mg increments) for study drug-related toxicities were permitted, with treatment to be discontinued if dose reduction below 100 mg was required, and doses could be interrupted for study drug-related toxicities for up to 28 days; specific guidelines on dose modifications are provided in the protocol.

RET alterations were identified via local testing methods including next-generation sequencing (NGS) of tumour or ctDNA in blood, or fluorescence in-situ hybridisation (FISH) of tumour tissue. CT or MRI of all known sites of disease was done at screening, approximately every 8 weeks during treatment, and, for patients who discontinued treatment without disease progression, every 3–4 months after the last dose. Adverse events were monitored from the start of treatment until 30 days after the last dose and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Clinical laboratory evaluations for safety were done at local laboratories according to the schedules specified in the protocol.

Outcomes

The primary endpoints of phase 1 were determination of the maximum tolerated dose and recommended phase 2

dose, and safety; secondary endpoints included overall response rates and other measures of antineoplastic activity by disease type, *RET* gene status, and previous treatment status where applicable, and pharmacokinetic and pharmacodynamic parameters of pralsetinib. In this Article, we report the following data from phase 1: occurrence of dose-limiting toxicities and their impact on maximum tolerated dose and recommended phase 2 dose determinations, and response outcomes in patients with *RET* fusion-positive NSCLC. Full outcomes of the phase 1 portion of this study will be presented in a later publication. The primary endpoints of phase 2 were the proportion of patients achieving an objective tumour response (a complete or partial response per RECIST 1.1) by blinded independent central review (central reviewing radiologists were masked to individual patient treatment status and assessments of response from local investigators) and safety. Secondary endpoints were duration of response (defined as the time from first tumour response until disease progression or death, whichever occurred first), clinical benefit rate (proportion of patients with a confirmed complete or partial response or stable disease lasting for ≥ 16 weeks), disease control rate (proportion of patients with a complete or partial response or stable disease), intracranial response rate, progression-free survival (defined as the time from first pralsetinib dose to disease progression or death, whichever occurred first), overall survival (defined as the time from first dose of pralsetinib to the date of death due to any cause), and electrocardiogram assessment (primary parameter QT interval corrected by means of Fridericia's formula; details included in appendix p 7). Assessment of tumour response outcomes by baseline *RET* fusion partner (per locally conducted assays and central ctDNA assay) was also a prespecified secondary endpoint. Pharmacokinetic parameters of pralsetinib, a secondary endpoint of ARROW will be presented in a later publication. Time to intracranial progression was added as a secondary endpoint in a protocol amendment (July 8, 2020) after the data cutoff and will be presented in a later publication.

Statistical analysis

A sample size of approximately 80 patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy was predicted to provide more than 95% power at the two-sided significance level of 0.05 for testing the null hypothesis of an overall response rate of 23% versus the alternative rate of 50%; a sample size of 170 patients with treatment-naïve *RET* fusion-positive NSCLC not previously treated with a platinum-based chemotherapy (enrolment ongoing) was predicted to provide more than 90% power at the two-sided significance level of 0.05 for testing the null hypothesis overall response rate of 48% versus the alternative rate of 61%.

Patients with *RET* fusion-positive NSCLC who received pralsetinib at the recommended phase 2 dose of 400 mg

	Previous platinum-based chemotherapy group (n=92)	No previous systemic treatment group (n=29)
Age, years	60 (63–68)	65 (54–69)
≥65 years	33 (36%)	15 (52%)
Sex		
Female	46 (50%)	15 (52%)
Male	46 (50%)	14 (48%)
Region		
USA	30 (33%)	7 (24%)
Europe	32 (35%)	14 (48%)
Asia	30 (33%)	8 (28%)
Race		
White	49 (53%)	17 (59%)
Asian	32 (35%)	10 (34%)
Other or unknown	11 (12%)	2 (7%)
Smoking history		
Current or former	32 (35%)	13 (45%)
Never or unknown	60 (65%)	16 (55%)
Histology		
Adenocarcinoma	88 (96%)	29 (100%)
Other*	4 (4%)	0
Eastern Cooperative Oncology Group performance status		
0	34 (37%)	11 (38%)
1	53 (58%)	17 (59%)
2†	5 (5%)	1 (3%)
Brain metastases‡	38 (41%)	12 (41%)
RET fusion partner		
KIF5B	69 (75%)	20 (69%)
CCDC6	16 (17%)	3 (10%)
Other	2 (2%)§	0
Unknown	5 (5%)¶	6 (21%)

(Table 1 continues on next column)

once daily (including patients enrolled in the phase 1 dose escalation) by the enrolment cutoff date (July 11, 2019) were included in the efficacy analyses; separate efficacy analyses were done for patients who had received previous platinum-based chemotherapy and for patients who were treatment naive and not candidates for available standard therapies. The findings presented herein represent updated interim analyses done in the registrational populations for regulatory filings. Tumour response endpoints (overall response rate, duration of response, clinical benefit rate, and disease control rate) were assessed for the *RET* fusion-positive measurable disease populations, which consisted of the subsets of patients in the efficacy populations with sufficient evidence of a *RET* fusion and baseline measurable disease confirmed on blinded independent central review. Time-to-event endpoints (progression-free survival and overall survival) were assessed in the full efficacy populations, defined as all patients who initiated pralsetinib 400 mg once daily by July 11, 2019. The enrolment cutoff date and definition for measurable

	Previous platinum-based chemotherapy group (n=92)	No previous systemic treatment group (n=29)
(Continued from previous column)		
RET assay**		
Next-generation sequencing -based	41 (45%)	8 (28%)
ctDNA	61 (66%)	16 (55%)
FISH	18 (20%)	9 (31%)
Other	7 (8%)	6 (21%)
Lines of previous therapy	2 (1–3)	0
Previous therapy type		
Chemotherapy	92 (100%)	0
PD-(L)1 inhibitor	41 (45%)	0
Multikinase inhibitor	24 (26%)	0

Data are median (IQR) or n (%). The efficacy population includes all patients with *RET* fusion-positive non-small-cell lung cancer who initiated 400 mg once daily pralsetinib by Jul 11, 2019. ctDNA=circulating tumour DNA. FISH=fluorescence in situ hybridisation. NGS=next-generation sequencing. PD-(L)1=programmed cell death-1 or programmed cell death-ligand 1. RET=rearranged during transfection. *Includes squamous, undifferentiated, and other not specified. †ECOG performance status of 2 was permitted before a protocol amendment (July 25, 2018). ‡History of or current. §EML4, n=1; DOK1, n=1. ¶Fusion present but specific partner unknown; subgroup consisted of five patients with unknown *RET* fusion partner (five assessed by FISH) where central analysis of ctDNA or tissue was not done or did not detect a specific *RET* fusion. ||Fusion present but specific partner unknown; subgroup consisted of six patients with unknown *RET* fusion partner (three assessed by FISH, three by other methods) where central analysis of ctDNA or tissue was not done or did not detect a specific *RET* fusion. **Fusion status was assayed by multiple techniques in some patients. Other assay types included nanoString nCounter (nanoString, Seattle, WA, USA) and unknown.

Table 1: Baseline characteristics

disease population were defined by agreement with the US Food and Drug Administration in order to ensure adequate follow-up time for the registrational dataset and to provide an adequate assessment of pralsetinib in relevant populations. Safety is presented for all patients with *RET* fusion-positive NSCLC who had initiated 400 mg once daily by the analysis cutoff date (including patients enrolled in the phase 1 dose escalation); an additional analysis of safety was done including all patients, regardless of tumour type and treatment history, who received pralsetinib at 400 mg once daily by the analysis cutoff date.

Two-sided 95% CIs were based on exact binomial distributions by means of the Clopper-Pearson method. Duration of response, progression-free survival, and overall survival were determined by means of the Kaplan-Meier method. Estimates of duration of follow-up for duration of response, progression-free survival, and overall survival were based on the inverse Kaplan-Meier method, with 95% CIs based on the Greenwood formula.

Subgroup analyses of overall response rate were done by previous treatment history (previous multikinase inhibitor use [yes or no] and previous programmed cell death protein 1 or programmed cell death ligand 1 [PD-(L)1] inhibitor use [yes or no]) and *RET* fusion

partner. We did a post-hoc analysis of response rates in patients with *RET* fusions identified by ctDNA analysis done locally at study sites. In addition, we did a post-hoc analysis of overall response in patients with a history of or current CNS metastases and prior platinum-based chemotherapy. Tumour response outcomes were also analysed on the basis of local investigator disease assessment. A prespecified analysis of safety by history of programmed cell death-1–programmed cell death-ligand 1 inhibitor treatment (yes or no) was done.

All statistical analyses were done with SAS version 9.4 (Cary, NC, USA). The data cutoff for all analyses was May 22, 2020. An independent data monitoring committee was established during the phase 2 study. This study is registered with ClinicalTrials.gov, NCT03037385.

Role of the funding source

The study was designed by the funder (Blueprint Medicines) in collaboration with the investigators. The funder collected, analysed, and interpreted the data in conjunction with the authors, who had access to all the raw data. Editorial support was provided by a medical writer, funded by the study funder.

Results

Between March 17, 2017, and the analysis cutoff date of May 22, 2020 (at which time the study was ongoing, and enrolment of patients with treatment-naïve *RET* fusion-positive NSCLC was ongoing), 587 patients were screened, of whom 521 patients were enrolled and received treatment. 471 patients (233 with *RET* fusion-positive NSCLC, 162 with medullary thyroid cancer, and 76 with other tumour types) received pralsetinib at the recommended phase 2 dose of 400 mg once daily across the dose escalation and dose expansion parts (appendix p 21). Of the 233 patients with *RET* fusion-positive NSCLC, 92 had previously received platinum-based chemotherapy and 29 were systemic treatment naïve and had initiated treatment with pralsetinib by the enrolment cutoff of July 11, 2019 (efficacy populations). Because six patients did not have baseline measurable disease confirmed by blinded independent central review and one had insufficient evidence of *RET* fusion, 87 who previously received platinum-based chemotherapy and 27 who were systemic treatment naïve were included in the *RET* fusion-positive measurable disease populations (appendix p 22).

Conduct of the phase 1 portion of the study per the Bayesian optimal interval design (irrespective of tumour type) and responses in the phase 1 portion of ARROW in patients with *RET* fusion-positive NSCLC at each dose amount are shown in the appendix (pp 9, 20). Two patients treated at 600 mg once daily had dose-limiting toxicities (hypertension and hyponatremia, both grade 3), and the maximum tolerated dose of pralsetinib on a once-daily schedule was determined to be 400 mg. Selection of 400 mg once-daily as the recommended phase 2 dose was

	Previous platinum group (n=87)	No previous systemic treatment group (n=27)†
Overall response rate	53 (61%; 50–71)‡	19 (70%; 50–86)
Disease control rate	79 (91%; 83–96)	23 (85%; 66–96)
Best overall response		
Complete response	5 (6%)	3 (11%)
Partial response	48 (55%)‡	16 (59%)
Stable disease	26 (30%)	4 (15%)
Progressive disease	4 (5%)	3 (11%)
Not evaluable	4 (5%)	1 (4%)
Median duration of response, months	NR (15.2–NE)	9.0 (6.3–NE)
Rate at 6 months	83%; 73–94	74%; 52–96
Rate at 12 months	74%; 61–87	26%; 0–52
Clinical benefit rate§	69% (58–79)	70% (50–86)

Data are n (%; 95% CI), n (%), or median (95% CI). NE=not estimable. NR=not reached. †Includes patients with non-small-cell lung cancer who initiated 400 mg pralsetinib once daily by July 11, 2019, and had measurable disease per Response Evaluation Criteria in Solid Tumours version 1.1 at baseline by blinded independent central review. ‡Group consisted of patients who were not candidates for platinum-based chemotherapy. §Includes two patients who continued treatment with partial responses pending confirmation. §Confirmed complete response, partial response, or stable disease with duration ≥16 weeks.

Table 2: Clinical activity endpoints in patients with measurable disease*

based on safety and pharmacokinetic outcomes from phase 1 presented previously.⁸

Patients with *RET* fusion-positive NSCLC in the efficacy population who had previously received platinum-based chemotherapy had received a median of two (IQR 1–3) previous therapies including PD-(L)1 inhibitors (41 [45%] of 92) or multikinase inhibitors (24 [26%]; table 1).

Among the patients who had previously received platinum-based chemotherapy, the response rate was 53 (61%; 95% CI 50–71) of 87 (including two responses that were pending confirmation at the time of the data cutoff and were subsequently confirmed). Five (6%) complete responses were observed (table 2). Outcomes per local investigator disease assessments were generally consistent with those based on central review (appendix p 10). Responses were observed irrespective of *RET* fusion partner, previous multikinase inhibitor treatment, and previous PD-(L)1 inhibitor treatment (figure 1; appendix pp 11, 23). In a post-hoc analysis, the overall response rate among patients with measurable disease who had *RET* fusions identified by local ctDNA analysis was 33 (56%; 42–69) of 59 patients, and the rate among patients with unknown fusion partners was three (60%; 15–95) of five patients. Overall, among the 51 patients with confirmed responses, 34 (67%) continued treatment at the time of the data cutoff, including all five with complete responses. Median time to first response was 1.8 months (IQR 1.7–1.9; measured as part of the duration of response analyses), and median duration of response was not reached (95% CI 15.2–not estimable) at a median follow-up from first response of 12.9 months (11.1–16.7; figure 2A). Tumour shrinkage

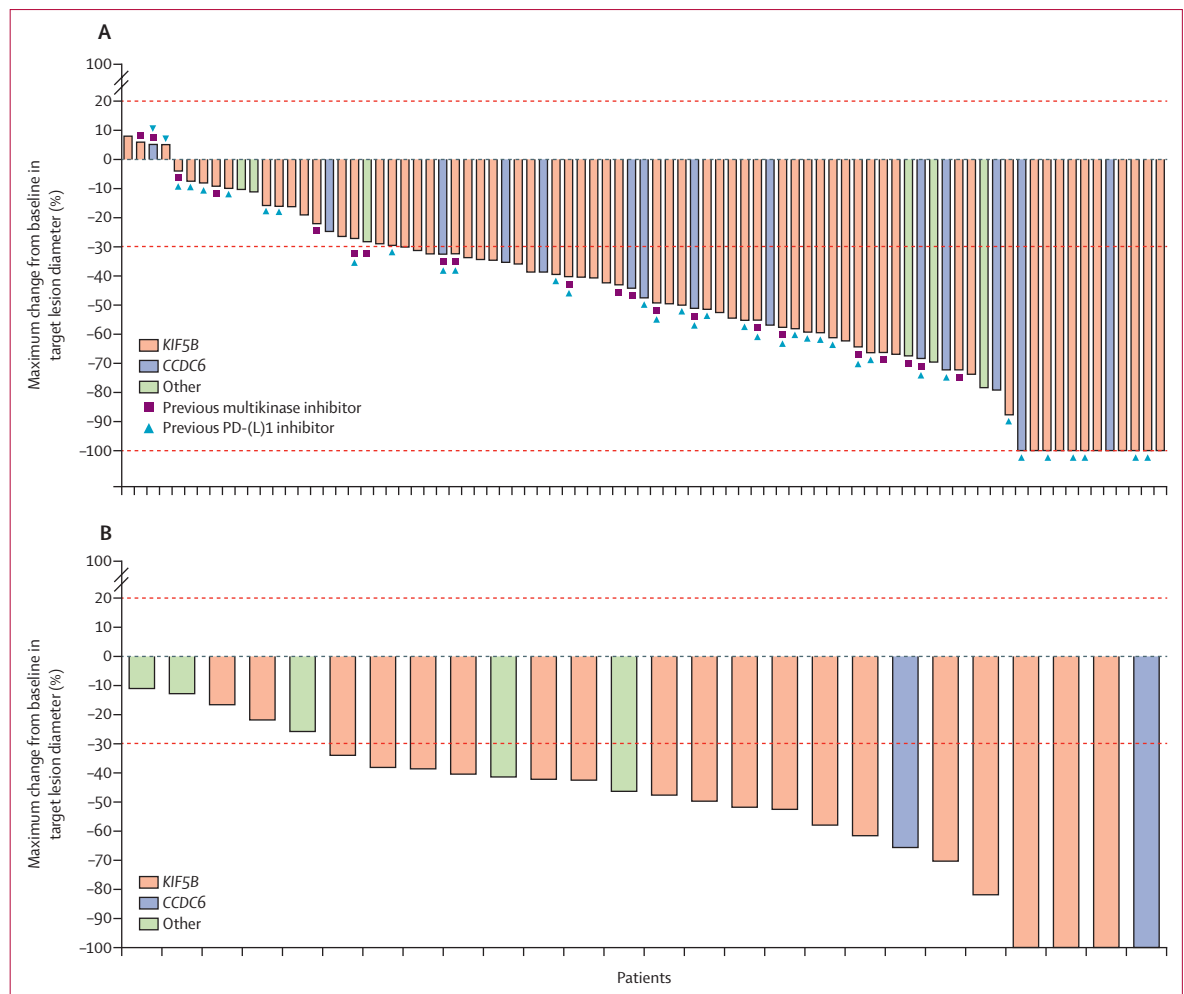


Figure 1: Maximum reduction in target lesion diameter in patients with previous platinum-based therapy (A) and patients with no previous systemic therapy (B). The dotted lines are positioned at +20%, -30%, and -100%; these represent the thresholds for progressive disease, partial response, and complete response per RECIST.

was observed in 79 (95%; 88–99) of 83 patients who had measurable disease and an evaluable post-baseline assessment. Median progression-free survival was 17.1 months (95% CI 8.3–22.1) at a median follow-up of 14.7 months (IQR 12.7–18.4; figure 2C); 42 (46%) patients had progression events or died. Median overall survival was not reached at a median follow-up of 17.1 months (IQR 14.6–20.3); 25 (27%) patients died.

Shrinkage of intracranial metastases was seen in all nine patients with measurable intracranial metastases at baseline and at least one post-baseline intracranial response assessment (all of whom had previous treatment for NSCLC, including one patient with only non-platinum-based previous systemic therapy; appendix p 24). Five of nine (56%; 95% CI 21–86) patients had an intracranial response, including three complete responses. Median duration of intracranial response was not reached. Kaplan-Meier estimates of the probability of ongoing intracranial response at 6 months was 80% (95% CI 45–100) and at 12 months was 53% (5–100). In a post-hoc analysis, the

overall response rate in patients with any history of CNS involvement and previous platinum-based treatment was 19 (51%; 34–68) of 37 patients.

In treatment-naïve patients who were not candidates for standard platinum therapies, 19 (70%; 95% CI 50–86) of 27 patients had a response, all of which were confirmed, including three (11%) complete responses. Response rates were consistent across *RET* fusion partners (figure 1); two (40%; 5–85) of five patients with unknown *RET* fusion partner had a response. Median duration of response in all responders was 9.0 months (95% CI 6.3–not estimable) at a median duration of follow-up of 10.2 months (IQR 7.8–11.8; figure 2B). Tumour shrinkage was observed in all 26 (100%; 95% CI 87–100) patients who had measurable disease and an evaluable post-baseline assessment. Median progression-free survival in treatment-naïve patients was 9.1 months (95% CI 6.1–13.0) at a median follow-up of 11.6 months (IQR 11.0–17.3; figure 2D); 17 patients (59%) had progression events or died. Overall survival was

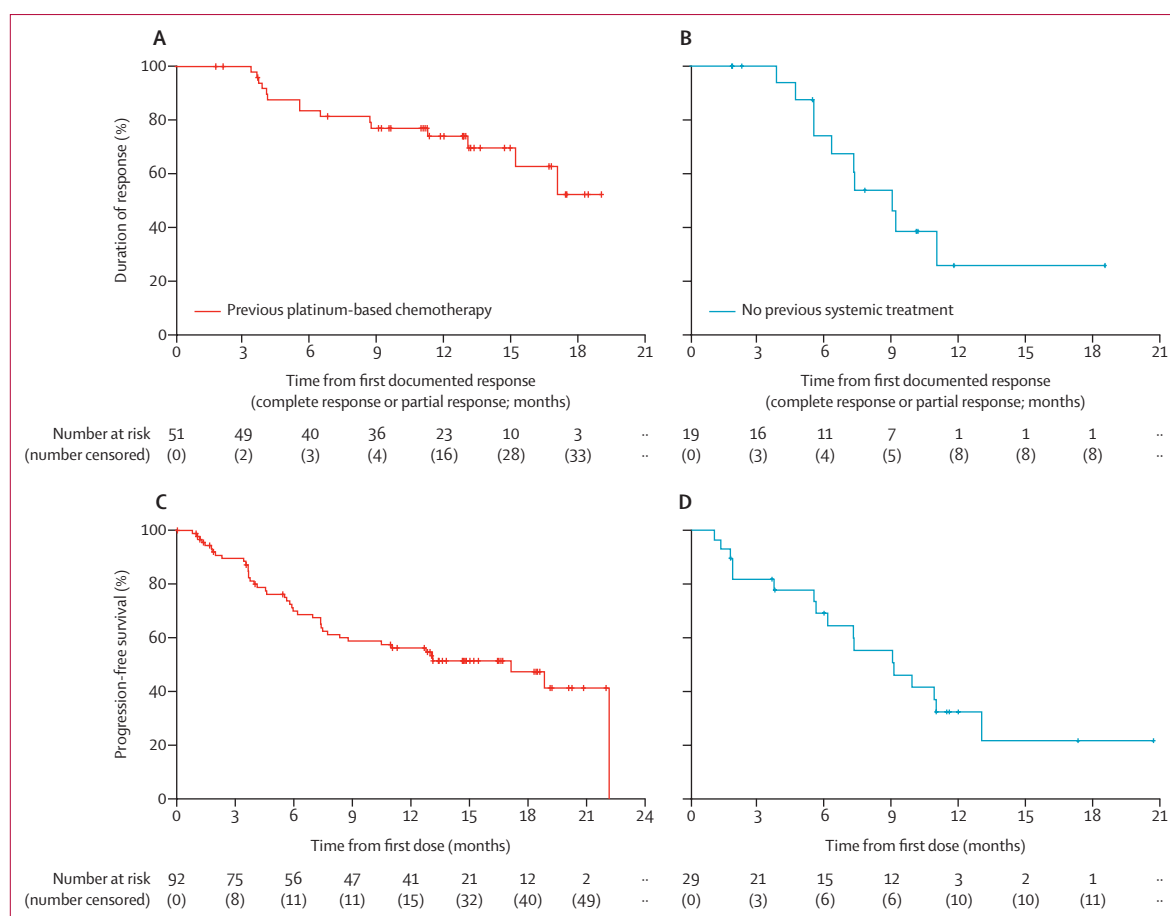


Figure 2: Kaplan-Meier analyses of duration of response (A–B) and progression-free survival (C–D) with pralsetinib in patients with *RET* fusion-positive non-small-cell lung cancer

not reached at a median follow-up of 13·6 months (IQR 13·0–17·6) with five deaths (17%).

Mean treatment duration in the NSCLC safety population (including all patients enrolled by the data cutoff; $n=233$) was 8·1 months (SD 6·0). Median relative dose intensity (the percentage of the planned 400 mg once-daily dosage received) was 95% (IQR 75–100). Overall, 216 (93%) patients had treatment-related adverse events, including 111 (48%) with grade 3 or worse treatment-related events. The most common grade 3 or worse treatment-related adverse events were neutropenia (in 43 [18%] of 233 patients), hypertension (26 [11%]), and anaemia (24 [10%]; table 3). Serious treatment-related adverse events were reported in 55 (24%) patients, the most frequent ($\geq 2\%$) were pneumonia (10 [4%]), pneumonitis (10 [4%]), anaemia (five [2%]), and neutropenia (five [2%]). 89 (38%) patients had dose reductions owing to treatment-related adverse events (appendix p 12). 14 (6%) patients discontinued treatment owing to a treatment-related adverse event (appendix p 13). There were no deaths considered related to pralsetinib. 40 (17%) of 233 patients with *RET* fusion-positive NSCLC had died by the data cutoff; 24 (10%) deaths occurred during the treatment-emergent period

(during or after administration of first pralsetinib dose until 30 days after last pralsetinib dose), of which ten (4%) were due to disease progression and 14 (6%) were due to other adverse events, and 16 (7%) occurred after the treatment-emergent period, of which 13 (6%) were due to disease progression, one ($<1\%$) to strong reduced general condition, and two (1%) for unknown reasons. Grade 3 or worse pneumonia was reported in 24 (10%) patients and grade 3 or worse pneumonitis was reported in four (2%) patients. Median neutrophil counts decreased gradually through week 4, but remained within the normal range ($>1500/\text{mm}^3$) and remained stable thereafter. Neutropenia leading to treatment interruption was reported in 39 (17%) patients or to dose reduction in 28 (12%) patients. Only one ($<1\%$) patient discontinued treatment owing to neutropenia. Four (2%) patients had febrile neutropenia, but none of these events resulted in treatment discontinuation. No patients had drug hypersensitivity considered related to pralsetinib.

The adverse event profile was generally similar between patients with and without previous programmed cell death-1–programmed cell death-ligand 1 inhibitor treatment (appendix p 15). The safety profile in all patients

	Grade 1–2	Grade 3	Grade 4
Neutropenia*	48 (21%)	34 (15%)	9 (4%)
Elevated aspartate aminotransferase	82 (35%)	4 (2%)	2 (1%)
Anaemia*	50 (21%)	24 (10%)	0
Decreased white blood cell count*	50 (21%)	14 (6%)	0
Elevated alanine aminotransferase	56 (24%)	4 (2%)	1 (<1%)
Asthenia*	49 (21%)	4 (2%)	0
Constipation	51 (22%)	2 (1%)	0
Hypertension*	24 (10%)	26 (11%)	0
Dysgeusia	31 (13%)	0	0
Elevated blood creatinine	30 (13%)	0	0
Thrombocytopenia*	23 (10%)	5 (2%)	2 (1%)
Diarrhoea	28 (12%)	1 (<1%)	0
Dry mouth	29 (12%)	0	0
Elevated blood creatine phosphokinase	19 (8%)	8 (3%)	0
Pneumonitis*	22 (9%)	3 (1%)	1 (<1%)
Hyperphosphataemia	25 (11%)	0	0
Lymphopenia*	14 (6%)	9 (4%)	2 (1%)
Oedema*	24 (10%)	0	0
Hypophosphataemia	6 (3%)	5 (2%)	1 (<1%)
Hyponatraemia*	6 (3%)	4 (2%)	1 (<1%)
Stomatitis	6 (3%)	4 (2%)	0

Data are n (%). Listed are adverse events of any grade reported in at least 10%, and of grade 3–4 reported in at least 2% of the 233 patients with *RET* fusion-positive non-small-cell lung cancer who initiated 400 mg pralsetinib and were deemed treatment-related by the investigators. No grade 5 treatment-related adverse events were reported in this population. *Grouped terms; adverse events that were similar were pooled together (eg, neutrophil count decreased and neutropenia).

Table 3: Treatment-related adverse events

who initiated pralsetinib 400 mg once daily by the analysis cutoff, irrespective of tumour type (n=471), is described in the appendix (pp 8, 17).

Pralsetinib had no clinically relevant or significant effect on QT interval prolongation (appendix pp 14, 25).

Discussion

The results of the ARROW study show that pralsetinib was well tolerated and showed clinical activity in patients with *RET* fusion-positive NSCLC, including intracranial responses, regardless of previous therapy, with response rates of 61% in patients who had received previous platinum chemotherapy and 70% in treatment-naïve patients who were not candidates for standard therapies.

RET fusions define a distinct molecular subset of NSCLC with characteristic clinical features. Initial efforts to develop targeted therapies for this patient population relied on drug repurposing strategies that made use of multikinase inhibitors with known ancillary anti-*RET* activity in addition to affinity for other kinases such as VEGFR2. In phase 2 trials, cabozantinib and lenvatinib showed low response rates (16–28%).^{2,4} Similarly, in two separate studies done in Japan and Korea evaluating the

activity of vandetanib in *RET* fusion-positive NSCLC, response rates were also modest (17% and 47%).^{3,5} Across all four studies, progression-free survival was short (4.5–7.3 months).^{2–5} Moreover, off-target toxicities led to dose reductions in 53–73% and drug discontinuation in 8–24%.^{2–4} A retrospective multicentre registry analysis of 53 patients with *RET* fusion-positive NSCLC treated with multikinase inhibitors in the real-world setting showed similar outcomes to the four previously mentioned studies, with response rates ranging from 18% to 37%.⁹ Owing to the low activity and toxicity concerns with multikinase inhibitors, treatment paradigms for advanced *RET* fusion-positive disease have been historically centred around platinum-based chemotherapy.¹⁰ *RET* fusion-positive NSCLC generally presents with low tumour mutational burden; in retrospective studies, patients have responded poorly to immune checkpoint inhibition.^{11,12}

In the ARROW study, pralsetinib showed rapid and durable clinical activity in patients with advanced *RET* fusion-positive NSCLC. In patients who previously received platinum-based chemotherapy, median progression-free survival was 17.1 months. Median duration of response was not yet reached, but the lower bound of the 95% CI was 15.2 months—attesting to the durability of response. Along with the response rate of 61%, these data are favourable when considered in the context of historical outcomes seen with therapies in the post-platinum-doublet setting for patients without targetable molecular drivers, where overall response rates range from 5% to 23%, and median progression-free survival does not exceed 4.5 months.^{13–18}

Pralsetinib also showed favourable activity in treatment-naïve patients who were not candidates for standard therapies. This patient group presented with several unfavourable prognostic factors at baseline, as might be expected in a population of patients who were not candidates for standard therapies. Median age was 65 years; for comparison, in the population of patients who received pralsetinib as second-line or later treatment after prior platinum therapy, the median age was 60 years with 59 (64%) of patients less than 65 years old. Furthermore, 12 (41%) of 29 treatment-naïve patients had brain metastases, a somewhat higher incidence than might be expected in a first-line metastatic population¹⁹ and the same as the post-platinum population (41%). Additionally, 13 (45%) were current or former smokers and the *RET* fusion partner was not identified in six (21%). Tumour shrinkage was observed in all evaluable treatment-naïve patients. The response rate (70%) observed with pralsetinib in this population is similar to rates seen with other targeted therapies in oncogene-driven lung cancers, including osimertinib in *EGFR*-mutant NSCLC (80%), alectinib in *ALK*-positive NSCLC (83%), and entrectinib (77%) and crizotinib (72%) in *ROS1* fusion-positive NSCLC.^{20–23} Together with data on selpercatinib,²⁴ the high response rates with

pralsetinib in treatment-naive patients further validate RET as a therapeutic target and solidify the overall targeted therapy paradigm in oncogene-driven NSCLC. Moreover, given the modest activity of platinum-doublet chemotherapies and checkpoint inhibitors in unselected patient populations^{25–28} and specifically in patients with *RET* fusion-positive NSCLC,^{11,12} findings from ARROW support a role for first-line selective RET inhibition with pralsetinib within this NSCLC treatment paradigm. Indeed, the US Food and Drug Administration has granted treatment-line-agnostic approval of pralsetinib²⁹ and selpercatinib³⁰ for the treatment of *RET* fusion-positive NSCLC.

The development of CNS metastases is common and a poor prognostic factor in patients with *RET* fusion-positive NSCLC.³¹ Preclinical studies of pralsetinib have shown blood–brain barrier penetration and activity against intracranial tumours.⁷ In the present study, pralsetinib showed intracranial activity in patients with *RET* fusion-positive NSCLC and measurable baseline brain metastases, including the inducement of intracranial complete responses.

Overall, pralsetinib was well tolerated at a dose of 400 mg once daily in patients with *RET* fusion-positive NSCLC, with adverse events being predominantly grade 1–2 in severity. Treatment-related adverse events leading to pralsetinib discontinuation were uncommon, occurring in 6% of patients in the safety population. Pralsetinib was associated with lower rates of adverse events classically attributed to VEGFR inhibition, such as hypertension, proteinuria, and palmar-plantar erythrodysesthesia, that are often observed in patients receiving multikinase inhibitor treatment.^{1–5} In preclinical enzymatic assays, pralsetinib was approximately 90 times more selective for RET than VEGFR2.⁶ Thus, the relative sparing of VEGFR2 from inhibition might contribute to the more favourable safety profile of pralsetinib compared with multikinase inhibitors. Neutropenia and anaemia are notable toxicities associated with immune checkpoint inhibitor–chemotherapy combinations.²⁵ Here, we observed relatively low rates of treatment-related grade 3 and worse anaemia and neutropenia (<20%). Overall, neutropenia generally occurred early after treatment initiation and was manageable, with 17% of patients requiring treatment interruption, 12% requiring dose reduction, and only one who discontinued treatment owing to neutropenia.

Although it is difficult to make cross-trial comparisons between different study populations, the overall frequency of adverse events with pralsetinib was generally similar to selpercatinib, although with a slightly different profile. Grade 3 or worse QT interval prolongation was reported in 4% of patients and of hypersensitivity were reported in 2% of patients, in a clinical trial of RETEVMO,³⁰ and are both safety warnings for selpercatinib, although neither were observed with pralsetinib in ARROW. Pneumonitis, reported as grade 3 or worse in 2% of patients with *RET* fusion-positive NSCLC in ARROW, is not a safety

warning for selpercatinib.³⁰ Rates of treatment-related hypertension were similar in the trial of selpercatinib and in the present study of pralsetinib.

It should be noted that although the populations evaluated in this study formed the basis for regulatory approval, the findings presented here are interim analyses; at the time of enrolment cutoff, target enrolment had not yet been reached. Another limitation of this study is that eligibility was determined by local assessment of *RET* fusion status through various testing methods. Despite the National Comprehensive Cancer Network recommendation for diagnostic *RET* testing,³² there is still no gold standard assay. We therefore allowed NGS (DNA or RNA from tumour tissue or DNA from plasma) or FISH for study entry. As *RET* FISH is unable to establish whether a *RET* rearrangement generates a functional, in-frame event, it is possible that a subset of the 13 patients with unspecified *RET* fusions (of whom six were in the treatment-naive population) might not have had functional, in-frame *RET* fusions; indeed, response rates were lower in the small number of treatment-naive patients with unknown fusion partner than in the overall treatment-naive population. Retrospective central confirmation of *RET* status by NGS of RNA from tumour tissue is ongoing. Evaluation of ctDNA dynamics following pralsetinib treatment is also ongoing, with preliminary analyses showing elimination of detectable *RET* fusion ctDNA in almost all patients assessed,³³ consistent with the broad clinical activity observed in the present analysis. Further data are being collected on comutations and resistance mutations arising in patients at the time of progression and will be analysed in the future. Of note, tumour mutational burden data were not collected routinely at all study sites, precluding meaningful analyses of response by this biomarker. The promising activity of pralsetinib supports implementation of molecular screening strategies for detection of *RET* rearrangements in patients with advanced NSCLC and other solid tumours.

In conclusion, we have shown that pralsetinib elicits clinically meaningful and durable responses in advanced *RET* fusion-positive NSCLC in both the treatment-naive and standard of care-refractory population, including intracranial responses, and has a manageable safety profile. These results not only show the activity of pralsetinib in advanced *RET* fusion-positive NSCLC, but also underscore the need to investigate selective RET inhibitors in other *RET*-altered tumours, outcomes for which are also being evaluated in the ongoing ARROW study.

Contributors

The study was designed by the funder in collaboration with all the authors. All authors contributed to data collection, which were analysed by HZ and the funder in conjunction with all the authors. All authors contributed to data interpretation. The first draft of the manuscript was written by JFG and VS with editorial support from a medical writer funded by the study funder. All authors had full access to all the data reported in the study, reviewed and edited the manuscript, and had final

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Declaration of interests

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Data sharing

The anonymised derived data from this study that underlie the results reported in this article will be made available, beginning 12 months and ending 5 years after this article's publication, to any investigators who sign a data access agreement and provide a methodologically sound proposal to medinfo@blueprintmedicines.com. The trial protocol will also be made available, as will a data fields dictionary.

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